

WHAT IS CLAIMED IS:

1. A method for monitoring the effect of a therapeutic composition on a mammal, comprising:

(i) measuring a first PAK phosphorylation level in a first biopsy obtained from said mammal before administration of a therapeutic composition to said mammal; and

(ii) measuring a second PAK phosphorylation level in a subsequent biopsy obtained from said mammal after administration of the therapeutic composition,

wherein a lower level of PAK phosphorylation in the subsequent biopsy compared to the first biopsy is indicative of an effect of the therapeutic composition on the mammal.

2. The method of claim 1, wherein the mammal is selected from the group consisting of a human, rat, mouse, pig, cow, goat, monkey, cat, and dog.

3. The method of claim 1, wherein the mammal is a human.

4. The method of claim 1, wherein the mammal has a disease.

5. The method of claim 4, wherein the disease is a cancer.

6. The method of claim 5, wherein the cancer is selected from the group consisting of thyroid cancer, colorectal cancer, pancreatic cancer, breast cancer, parotid cancer, synovial cell cancer, prostate cancer, laryngeal cancer, testicular cancer, hepatocellular cancer, and leiomyosarcoma.

7. The method of claim 1, wherein either or both of the biopsies are suspected of containing cells capable of anchorage-independent cell growth.

8. The method of claim 1, wherein neither the first nor the second biopsy is suspected of containing cells capable of anchorage-independent cell growth.

9. The method of claim 1, wherein either biopsy is a tissue biopsy.
10. The method of claim 9, wherein the tissue is buccal mucosa tissue, skin, hair follicles, tumor tissue, or bone marrow.
11. The method of claim 1, wherein either biopsy is a biological fluid.
12. The method of claim 11, wherein a biopsy is selected from synovial fluid, whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, and saliva.
13. The method of claim 1, wherein the therapeutic composition effects a change in one or more of physiological, biochemical, genetic, cellular, or immunological traits of the mammal.
14. The method of claim 1, wherein the first and subsequent biopsies are taken from a tumor in the mammal.
15. The method of claim 1, wherein the therapeutic composition directly or indirectly modulates the phosphorylation of at least one PAK.
16. The method of claim 1, wherein the phosphorylation of any combination of PAK4, PAK5, or PAK6 is measured.
17. The method of claim 1, wherein the phosphorylation of PAK4 is measured.
18. The method of claim 1, wherein a first level of phosphorylated PAK in the first biopsy obtained from the mammal is measured at least 1 day before administering the therapeutic composition to said mammal.
19. The method of claim 1, wherein a first level of phosphorylated PAK in the first biopsy obtained from the mammal is measured at least 5 days before administering the therapeutic composition to said mammal.

20. The method of claim 1, wherein a first level of phosphorylated PAK in the first biopsy obtained from the mammal is measured at least 14 days before administering the therapeutic composition to said mammal.

21. The method of claim 1, wherein administration of the therapeutic composition comprises at least one dose of the therapeutic composition.

22. The method of claim 1, wherein administration of the therapeutic composition comprises a regime of multiple doses of the therapeutic composition.

23. The method of claim 22, wherein the doses are administered during a period of 4 hours up to about 100 days.

24. The method of claim 1, wherein the subsequent biopsy is obtained from the mammal after administration of the final dose of said therapeutic composition.

25. The method of claim 22, wherein multiple biopsies are obtained from the mammal during the regime.

26. A method for selecting a mammal amenable to treatment with a PAK activity modulator, comprising measuring the level of phosphorylated PAK in a test biopsy obtained from a candidate mammal, wherein a level of phosphorylated PAK in the test biopsy that is greater than the level of phosphorylated PAK in a control biopsy indicates that the mammal is amenable to treatment with a PAK activity modulator.

27. The method of claim 26, wherein the candidate mammal is selected from the group consisting of a human, rat, mouse, pig, cow, goat, monkey, cat, and dog.

28. The method of claim 26, wherein the mammal is a human.

29. The method of claim 26, wherein the control biopsy is obtained from the same tissue type as the candidate mammal's test biopsy.

30. The method of claim 29, wherein the control biopsy is obtained from a healthy mammal of the same species as the candidate mammal.

31. The method of claim 29, wherein the tissue type is lymphocyte cells.

32. The method of claim 29, wherein the tissue type is brain, heart, lung, breast, skin, intestinal, colon, stomach, bladder.

33. The method of claim 26, wherein the mammal comprises a cancer cell.

34. A method for selecting a mammal amenable to treatment with a PAK activity modulator, comprising:

(i) determining the ratio of phosphorylated PAK to total PAK4 protein in a test biopsy of a tissue from a candidate mammal; and

(ii) comparing the ratio of (i) to the ratio of phosphorylated PAK to total PAK4 protein in a control biopsy that is obtained from the same tissue type as the candidate mammal's test biopsy,

wherein the candidate mammal is amenable to treatment with a PAK activity modulator if the ratio of phosphorylated PAK to total PAK4 protein in the test biopsy is greater than that of the control biopsy.

35. The method of claim 34, wherein the control biopsy is obtained from a healthy mammal of the same species as the candidate mammal.

36. The method of claim 34, wherein the candidate mammal comprises a cancer cell.

37. The method of claim 34, wherein the candidate mammal has a tumor.

38. The method of claim 34, wherein the level of phosphorylated PAK is determined by using a phosphospecific antibody specific to the phosphorylated serine of PAK4; and wherein the level of total PAK4 protein is determined using a PAK4-

specific antibody.

39. The method of claim 38, wherein the PAK4-specific antibody is raised against the peptide sequence, ATTARGGPGKAGSRGRFAGHSEA.

40. A method for selecting from a population of mammals that have cancer, a mammal that is amenable to treatment with a PAK activity modulator, comprising:

(i) determining a first level of phosphorylated PAK in a tumorigenic biopsy obtained from a tissue from a candidate mammal;

(ii) determining a second level of phosphorylated PAK in a non-tumorigenic biopsy of the same tissue from the candidate mammal of (i); and

(iii) comparing the first and second levels of phosphorylated PAK,

wherein a level of PAK phosphorylation that is greater in the first level than the second level indicates that the candidate mammal is a mammal that is amenable to treatment with a PAK activity modulator.

41. The method of claim 26, wherein the level of phosphorylated PAK is measured using a phosphospecific antibody specific for PAK.

42. The method of claim 41, wherein the phosphospecific antibody is raised against the peptide, RRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

43. The method of claim 34, wherein the level of phosphorylated PAK is measured using a phosphospecific antibody specific for PAK.

44. The method of claim 43, wherein the phosphospecific antibody is raised against the peptide, RRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

45. The method of claim 38, wherein the level of phosphorylated PAK is measured using a phosphospecific antibody specific for PAK.

46. The method of claim 45, wherein the phosphospecific antibody is raised against the peptide, RRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

47. A method for determining the level of phosphorylated PAK in a mammalian biopsy, comprising:

- (i) exposing the biopsy to a phosphospecific antibody specific for PAK; and
- (ii) detecting the antibody,

wherein the level of antibody detected correlates with the level of phosphorylated PAK in the mammalian biopsy.

48. The method of claim 47, wherein the phosphospecific antibody is raised against the peptide, RRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

49. A phosphospecific antibody raised against serine 474 of a PAK4 peptide.

50. The phosphospecific antibody of claim 49, wherein the PAK4 peptide comprises the amino acid sequence, KEVPRRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

51. A method of identifying a compound that modulates PAK phosphorylation, comprising:

- (i) adding a test compound to a preparation of PAK4 protein;
- (ii) measuring the level of phosphorylation of said PAK4 using a phosphospecific antibody directed against PAK4; and

(iii) comparing the level of the treated PAK4 preparation to the phosphorylation level of an untreated PAK4 preparation,

wherein a level of phosphorylation in the treated preparation that differs from the phosphorylation level of the untreated preparation indicates that the test compound is a compound that modulates PAK phosphorylation.

52. The method of claim 51, wherein the PAK4 preparation comprises PAK4 isolated from a biopsy from a mammal.

53. The method of claim 51, wherein the PAK4 preparation comprises recombinantly-produced PAK4 protein.

54. A method of identifying a compound that modulates PAK phosphorylation, comprising:

(i) exposing a culture of cells to a test compound;

(ii) measuring the level of phosphorylation of PAK using a phosphospecific antibody directed against PAK4; and

(iii) comparing that level to the level of PAK phosphorylation in untreated cells,

wherein a level of phosphorylation that is lower or higher than the untreated cells indicates that the test compound is a compound that modulates PAK phosphorylation.

55. The method of claim 54, wherein the phosphospecific antibody is raised against the peptide, RRKSLVGTPYWMAPE, which comprises a phosphorylated serine.

56. A method for selecting a mammal amenable to treatment with a PAK activity modulator, comprising determining whether PAK4 protein is overexpressed in a biopsy obtained from the mammal, wherein a level of PAK4 protein that is

greater than the normal level of PAK4 expression in an equivalent biopsy sample indicates that the mammal is amenable to treatment with a PAK activity modulator.

57. The method of claim 56, wherein the level of PAK4 protein is determined using a PAK4-specific antibody.

58. The method of claim 57, wherein the PAK4-specific antibody is raised against the peptide sequence, ATTARGGPGKAGSRGRFAGHSEA.

59. A method for selecting a mammal amenable to treatment with a PAK activity modulator, comprising:

(i) measuring the level of PAK4 protein in a biopsy obtained from a first tissue of an organ of a candidate mammal;

(ii) measuring the level of PAK4 protein in a biopsy obtained from a second tissue of the organ of a candidate mammal; and

(iii) comparing the two levels,

wherein a difference between the levels of PAK4 protein in the two biopsies indicates that the candidate mammal is amenable to treatment with a PAK activity modulator.

60. The method of claim 59, wherein the level of PAK4 protein is determined using a PAK4-specific antibody.

61. The method of claim 60 wherein the PAK4-specific antibody is raised against the peptide sequence, ATTARGGPGKAGSRGRFAGHSEA.

62. A method for selecting a mammal amenable to treatment with a PAK activity modulator, comprising:

(i) determining whether PAK4 mRNA is overexpressed in a biopsy from a tissue obtained from a candidate mammal,

wherein a level of PAK4 mRNA that is greater than the normal level of PAK4 mRNA expression in a biopsy obtained from an equivalent tissue from a known healthy mammal indicates that the candidate mammal is amenable to treatment with a PAK activity modulator.